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METABOLISM OF FISSION PRODUCTS

Progress Report for Period Ending April 15, 1944

by

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ABSTRACT

RADIOZIRCONIUM

Preparation of Carrier-Free Zr^{93}

The Zr^{93} was prepared from neutron bombarded $UO_2(NO_3)_2 \cdot 6H_2O$. The Zr^{93} was removed from most of the fission products by the iodate method. Further purification was made using HF, and the Zr^{93} was finally purified by repeated K_2CO_3 fusions.

Tracer Studies

Radiozirconium without carrier is absorbed very poorly following parenteral administration. Approximately 40% of the absorbed fraction is deposited in the skeleton. Excretion is slow, chiefly by way of the digestive tract, and the estimated interval of time required for half of the absorbed carrier-free radiozirconium to be excreted is of the order of 80 days. Retention by the lung following intrapulmonary administration is the highest for all of the fission products, ranging from 92% at four days to 62% at 64 days. Absorption by way of the digestive tract is less than 0.01%.

RADIOYTTRIUM (Y^{88})

Intramuscular studies with carrier-free Y^{88} revealed results similar in character to the earlier intraperitoneal experiments except for much less retention of the administered activity by the intraperitoneal organs. Intrapulmonary experiments revealed a moderate degree of lung retention of activity which ranged from 83% at one day to 6.4% at 64 days after administration. Most of the absorbed Y^{88} was deposited in the skeleton.

RADIOCERIUM ($Ce^{>140}$)

Intramuscular experiments with carrier-free $Ce^{>140}$ (Ce^3) were undertaken to supplement earlier $Ce^{>140}$ intraperitoneal and incomplete intramuscular studies. These studies indicated that while carrier-free radiocerium is deposited chiefly in the skeleton, a relatively high uptake occurs in the liver and the rate of elimination apparently is significantly greater than for carrier-free radioyttrium. The lung retention of $Ce^{>140}$ following intrapulmonary administration is somewhat greater than with Y^{88} and ranges from 67% at 1 day to 9.4% at 64 days after administration. The metabolic behavior of the carrier-free radioactive isotopes of lanthanum, cerium, and praseodymium are quite similar and differ significantly from carrier-free radioyttrium.

DECONTAMINATION STUDIES

Age Effect

Young growing rats, in which calcification is active, retained over twice as much radiostrontium as did the old adult animals.

Carrier Strontium

Repeated doses of nonradioactive strontium increased the excretion of radiostrontium almost 50%, but only when the therapy was commenced immediately after the injection of radiostrontium.

Parathormone

Large doses of parathormone (at toxic levels) caused a small increase in the excretion of radiostrontium, but the value of this hormone in acute therapy is questionable.

Irradiated Sterols

Massive toxic doses of irradiated ergosterol or of Hytakerol had no effect on the retention of radiostrontium. The small increase in urinary excretion was more than balanced by a decrease in fecal elimination.

Calcium Content of the Diet

Rats on a low calcium diet showed a decrease in the urinary excretion of radiostrontium and radiocerium, but the increased retention by these animals was small. No effect was observed with radioyttrium.

PREPARATION OF Zr^{93} FREE FROM INERT CARRIER

Outline of Method

The radiozirconium was isolated from neutron bombarded $UO_2(NO_3)_2 \cdot 6H_2O$. The bulk of the uranyl nitrate was removed by ether extraction. Zirconium and the other ammonia-insoluble fission products were separated from the remaining uranyl nitrate by complexing the uranium salt with hydroxylamine in ammoniacal solution, the insoluble fission products being carried down on $Fe(OH)_3$. Zirconium, columbium, and cerium were separated as the iodates using thorium carrier. Zirconium and columbium were separated from cerium and thorium by means of HF. Columbium was removed from the zirconium by repeated fusions with K_2CO_3, again using thorium as hold-back carrier for the zirconium. The thorium was finally separated from the zirconium by precipitation with HF.

Procedure

The source of the sample of radiozirconium described here was a 60-lb batch taken from 350 lbs of $UO_2(NO_3)_2 \cdot 6H_2O$ which had been bombarded with 10,000 microampere hours of Li neutrons and 80,000 microampere hours of Be neutrons (March to July, 1943).

The amount of uranyl nitrate was reduced to 5 mg by means of repeated ether extractions. The concentrated solution of fission products was treated with 100 mg of Fe and 15 g of $HN_2OH \cdot HCl$ and made strongly alkaline with NH_4OH. The mixture was heated to boiling, cooled, and the iron precipitate was centrifuged out. The $Fe(OH)_3$ was dissolved in HCl and reprecipitated twice more in the presence of $NH_2OH \cdot HCl$. The final iron precipitate was dissolved in HNO_3 and 25 mg of thorium were added to the solution. The solution was then made 5N in HNO_3 and the thorium was precipitated as the iodate using an equal volume of .35M KIO_3 reagent. The iodate precipitate was centrifuged out and washed with dilute

KIO_3 solution. The precipitate was decomposed by repeated evaporations with concentrated HCl and finally evaporated to dryness.

The residue was dissolved in 20 cc of 5N HNO_3 and 5 mg each of barium, strontium, yttrium, tellurium, ruthenium, cesium, and lanthanum were added. The thorium was again precipitated by the addition of 20 cc of KIO_3 reagent and centrifuged out. The thorium iodate precipitate was washed and decomposed with HCl as before. The final residue was dissolved in 1N HCl and 10 mg of cerium were added. The solution was made 2N in HF and the cerium fluoride precipitate was centrifuged out, washed, and discarded. The supernatant liquid and washings were combined and evaporated to fuming with 1 cc of concentrated H_2SO_4.

The solution was diluted to about 40 cc and 10 mg of thorium were added. The solution was made basic with NH_4OH and the $Th(OH)_4$ was centrifuged out and washed. The precipitate was evaporated to dryness and fused with 4 g of K_2CO_3. The fused mass was cooled and taken up in 10 cc of water. The resulting suspension was centrifuged and the residue was washed once with 10 cc of 30% K_2CO_3 solution. The supernatant liquid and washings were combined and set aside for the Cb^{93} separation.

The residue from the K_2CO_3 fusion (ThO_2) was fumed with 2 cc of concentrated H_2SO_4 for about 15 minutes. The mixture was cooled and diluted to 30 cc with ice water. Five mg of columbium were added and the solution was made alkaline with NH_4OH. The resulting precipitate was centrifuged out and washed. The washed precipitate was dried and again subjected to the Zr-Cb separation by means of fusion with K_2CO_3. The thorium oxide residue (containing the Zr^{93}) was once more taken through the Zr-Cb separation by means of K_2CO_3 fusion, but without the addition of Cb carrier. The final thorium oxide residue was brought into solution with H_2SO_4 as described previously and the solution was diluted to 40 cc. The solution was made 2N in HF and the thorium fluoride precipitate was centrifuged out and washed with dilute HF.

The combined supernatant liquid and washing from the fluoride precipitate were evaporated to fuming and then diluted. Ten mg of Fe were added and the solution was made basic with HN_4OH. The iron precipitate was centrifuged out, washed, and dissolved in 15 cc of 9N HCl. The Fe was extracted with isopropyl ether. This final solution of Zr^{93} contained a total of 203 microcuries (measured four months after the conclusion of the bombardment). The activity was measured with a Lauritsen electroscope whose window and air gas from the sample was equivalent to 4 mg/cm^{-2}.

Twenty-four hours after the completion of the zirconium preparation a suitable aliquot was taken for an assay. Ten mg each of zirconium and columbium were added to the aliquot and the elements were then separated chemically. 3.3% of the activity was found to be associated with the columbium fraction. The Zr^{93} fraction (96.7% of activity) was used for the determination of an Al absorption curve.

An aliquot of the final zirconium solution was taken for a test of radioactive purity. Ten mg each of zirconium, strontium, barium, thorium, yttrium, cerium, lanthanum, ruthenium, tellurium, and cerium were added to the aliquot. The solution was made 3N in HCl in a volume of 50 cc. One cc of 85% of H_3PO_4 was added and the mixture was boiled for 30 minutes. The precipitate of zirconium phosphate was centrifuged out and washed. Ten mg more of zirconium were added to the combined supernatant liquid and washing and the mixture was boiled again. The second zirconium phosphate precipitate was centrifuged out and washed. The combined supernatant liquid and washings were evaporated to dryness in a porcelain dish. The zirconium phosphate precipitates were combined and also taken to dryness in a porcelain dish. The activities of the two fractions were measured with an electroscope with a thin window. It was found that 99.8% of the total activity was associated with the zirconium (and columbium) fraction.

The absorption curve is shown in Figure 1. Four months have elapsed since the preparation of the Zr^{93} sample which is not sufficient at this time for an accurate check of its half-life.

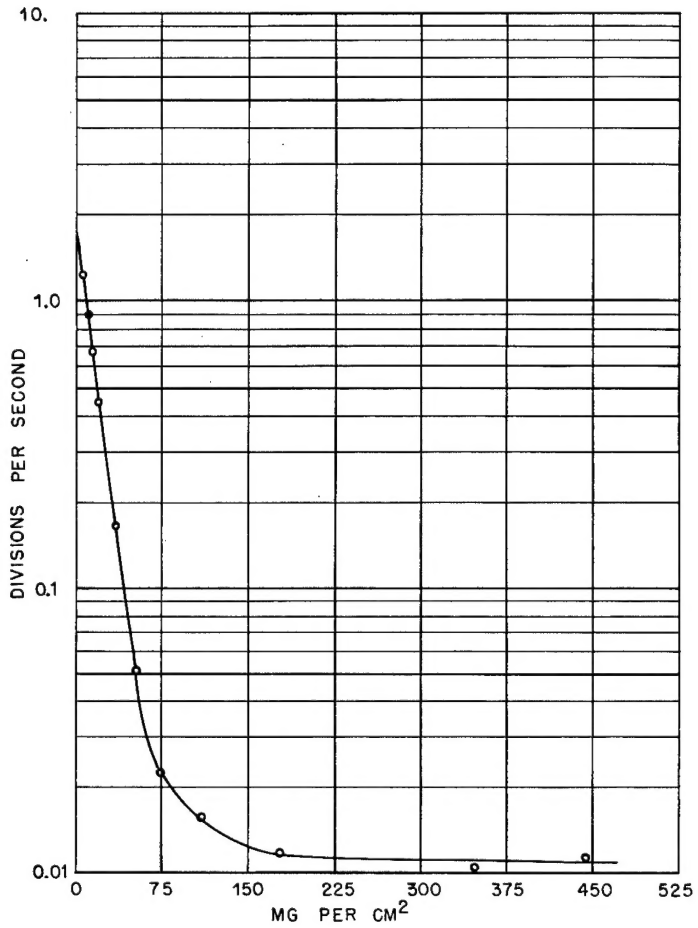

Figure 1. Al absorption curve for Zr^{93}—half value thickness = 10.1 mg/cm^2.

METABOLISM OF CARRIER-FREE RADIOZIRCONIUM FOLLOWING INTRAMUSCULAR, INTRAPULMONARY, AND ORAL ADMINISTRATION

Method

The carrier-free Zr^{93} was injected as the chloride in an isotonic solution of sodium chloride at pH 2.5 into the following groups of three rats each: three intramuscular and three intrapulmonary. Carrier-free Zr^{89} was injected as the chloride in an isotonic solution of sodium chloride at a pH of 2.7 into the following groups of three rats each: two intraperitoneal, two intramuscular, one intrapulmonary, and one oral. The method for the isolation and purification of Zr^{89} appears in report No. CH-498. The animals receiving Zr^{93} were sacrificed at the following time intervals: 1, 4, and 32 days for the intramuscular groups, and 1, 32, and 64 days for the intrapulmonary groups. The animals receiving Zr^{89} were sacrificed at the following time intervals: 4 and 16 days for the intraperitoneal and intramuscular, 4 days for the intrapulmonary, and 4 days for the oral. The tissues and excreta were collected, ashed, and measured as has been described in previous reports. In the case of the samples containing Zr^{93}, an interval of from 2 1/2 to 3 1/2 months was allowed to elapse between the time that the samples were collected and the date that they were measured. This was done in order to permit the decay of the Cb^{93}, formed by growth from Zr^{93}, which was produced in the tissues during the interval of time that the Zr^{93} was in the animals. Suitable mass absorption curves were secured for both zirconium isotopes, and the appropriate corrections applied to the measured samples. No evidence of volatilization of the active zirconium was observed following ashing of the tissues at 500°C.

Table 1. Distribution of Zr^{89} without carrier following intramuscular administration.

	Four days		Sixteen days	
	% per organ	% per gram	% per organ	% per gram
Heart	.036	.038	.013	.012
Liver	1.105	.11	.77	.073
Kidney	.55	.24	.32	.13
Testes	.18	.045	.19	.056
Spleen	.15	.11	.10	.11
Muscle[1]	1.31	.011	1.02	.008
Skin[2]	1.66	.039	.90	.002
Stomach	.062	.018	.055	.013
Sm. intestine	.45	.026	.20	.017
Lg. intestine	.026	.042	.014	.016
Bone[3]	7.39	.307	11.92	.42
Brain	.004	.003	.003	.003
Lungs	.088	.056	.072	.039
Unab. in left leg	86.34		78.03	
Fat		.034		.002
Blood[4]	1.81	.082	.27	.013
Adrenals	.001	.029	.005	.034
Lymph glands		.050		.025
Feces[5]		.019		.02
Balance[6]	3.90		3.64	
Total urine	.33		1.29	
Total feces	.86		2.43	
Recovery	101.47		99.04	

[1] Muscle estimated as 45% of total body weight.

[2] Skin estimated as 42 grams.

[3] Measured value for entire skeleton.

[4] Blood estimated as 8% of total body weight.

[5] Specimen of feces removed from large intestines at time of sacrifice.

[6] Balance is measured value for carcass less skeleton but includes skin, blood, and muscle.

Results

It will be noted from data in Tables 1 and 2 that most of the zirconium administered by intramuscular injection remained unabsorbed at the site of administration.

Table 2. Distribution of Zr^{93} without carrier following intramuscular administration.

	One day			Four days		Thirty-two days	
	% per organ	% per gram		% per organ	% per gram	% per organ	% per gram
Heart	.018	.024		.015	.024	.017	.021
Liver	.42	.036		.52	.075	.53	.052
Kidney	.075	.040		.21	.15	.35	.15
Ovaries	.004	.033	Testes	.075	.028	.16	.057
Spleen	.011	.019		.030	.046	.055	.072
Muscle[1]	.44	.0048		.75	.0099	1.30	.012
Skin[2]	.55	.013		.84	.020	.87	.021
Stomach	.019	.008		.032	.013	.025	.010
Sm. intestine	.11	.011		.15	.021	.24	.017
Lg. intestine	.011	.012		.017	.033	.016	.034
Bone[3]	.51	.032		3.62	.27	8.57	.48
Brain	.005	.003		.005	.004	.006	.005
Lungs	.030	.030		.049	.039	.057	.038
Unab. in left leg	85.52			97.21		81.54	
Fat		.008			.014		.016
Blood[4]	1.44	.090		.73	.055	.28	.015
Adrenals	.001	.016		.001	.022	.001	.01
Lymph nodes		.021			.033		.074
Balance[5]	6.04			7.38		4.52	
Total urine	3.5			.33		2.36	
Total feces	.30			1.07		5.59	
Recovery	106.57%			110.70%		104.03%	

[1]Muscle estimated as 45% of total body weight.

[2]Skin estimated as 42 grams.

[3]Measured value for entire skeleton.

[4]Blood estimated as 8% of total body weight.

[5]Balance is measured value for carcass less skeleton but includes skin, blood, and muscle.

Even at the 32-day interval approximately 80% remained unabsorbed. The skeleton shows the greatest degree of total uptake and also the highest specific activity on a per gram basis except at the 1-day interval. Kidney is the next most active tissue on the per gram basis. The elimination of zirconium is relatively slow. At the 32-day interval, approximately 1/3rd of the absorbed fraction is excreted and the digestive tract acts as the chief channel of elimination (Tables 3 and 4). The intraperitoneal experiments are not shown in the tables due to the fact that most of the administered dose

apparently was deposited upon the surfaces of the intraperitoneal organs. Obviously, such results give no true indication of the normal metabolic pattern of zirconium in structures such as liver, kidney, spleen, etc. The uptake by the skeleton in the intraperitoneal experiments was approximately the same as was noted in the intramuscular studies.

The oral absorption from the digestive tract of Zr^{89} with carrier was less than 0.01%.

The intrapulmonary studies indicate that the retention of zirconium by the lungs is the highest of all of the fission products ranging from 80 to 90% at the 1- and 4-day intervals to 62% at 64 days (Table 5). The distribution pattern of the absorbed fraction was very similar to that noted in the intramuscular studies for the corresponding time intervals.

Radioautographic studies of the lungs following Zr^{93} administration have not as yet been completed, but the results in hand indicate that this material is distributed in an irregular and diffuse pattern with no significant localization in the bronchial tree, blood vessels, or lymph tissues. Representative photomicrographs of both the sections and their radioautographs will appear later in a separate report.

Discussion

The distribution of zirconium following intramuscular administration bears a closer resemblance to the metabolic behavior of the rare earths than to the metabolic behavior of columbium in that the soft tissue content of the absorbed fraction of the latter element tends to be higher. The rate of elimination of zirconium indicates that the approximate half-time of retained activity in the body is of the order of 80 days. This value is, of course, a very crude approximation, but it appears that the elimination of absorbed zirconium following intramuscular administration is less than its rate of radioactive decay.

It will be noted that the daily rate of both urinary and fecal excretion of zirconium following intramuscular injection does not significantly change throughout the entire period of the experiments. This observation is in variance with the results noted for alkaline earths, rare earths, columbium, etc. A possible explanation for this behavior of zirconium is that the injected material was absorbed both slowly and at a relatively constant rate from the site of administration

Certain differences may be noted between the 4-day intramuscular experiments with Zr^{89} and the corresponding studies at four days with Zr^{93}. Apparently with Zr^{89} approximately twice as much

Table 3. Excretion per day of administered dose of Zr^{89} without carrier following intramuscular injection.

Time (days)	Urine	Feces
1	.28%	.08%
2	.08%	.10%
3	.07%	.19%
4	.08%	.25%
5	.10%	.23%
6	.03%	.12%
7	.06%	.26%
8	.09%	.11%
9	.07%	.17%
10	.03%	.19%
11	.03%	.19%
12	.01%	.22%
13	.03%	.10%
14	.004%	.13%
15	.02%	.29%
Total	.98%	2.63%

Table 4. Excretion per day of administered dose of Zr^{93} without carrier following intramuscular injection.

Time (days)	Urine	Feces
1	.18%	.19%
2	.09	.17
3	.08	.21
4	.08	.29
5	.09	.26
6	.04	.10
7	.05	.20
8	.07	.08
9	.07	.15
10	.05	.16
11	.06	.12
12	.04	.16
13	.05	.10
14	.02	.24
15	.07	.07
16	.06	.18
17	.06	.18
18	.08	.13
19	.08	.13
20	.09	.11
21	.09	.11
22	.04	.18
23	.06	.41
24	.06	.41
25	.12	.16
26	.12	.16
27	.10	.13
28	.10	.13
29	.10	.10
30	.10	.18
31	.10	.18
32	.13	.49
Total	2.53%	5.87%

Table 5. Distribution of retained activity following intrapulmonary administration of Zr^{89} and Zr^{93}.

	1 day (Zr^{93})		4 days[5] (Zr^{89})		32 days (Zr^{93})		64 days[5] (Zr^{93})	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Liver	.82	.06	.36	.03	.50	.04	1.14	.12
Kidney	.13	.06	.20	.08	.29	.12	.60	.25
Spleen	.1	.1	.27	.38	.36	.50	.65	.96
Skin[1]	omitted		.58	.01	.86	.025	2.96	.09
G-I tract[2]	omitted		omitted		1.87	.056	1.55	.09
Bone[3]	10.2	.50(est)	3.85	.21	16.3	1.08	16.3	.98
Lungs	77.9	54.4	92.2	50.3	75.9	53.0	62.0	31.0
Balance[4]	12.3		1.68		3.60		14.9	

[1] Animals skinned, measured value for entire skin.
[2] G-I tract removed and assayed as a unit.
[3] Measured value for entire skeleton.
[4] Measured value for remaining carcass less skin and skeleton but including blood and muscle.
[5] Two animals used in experiment.

of the administered dose was absorbed at the site of injection and all of the tissues show a correspondingly high uptake although the ratio of the activities between the different tissues is comparable in both experiments.

It will be noted in all of the intramuscular experiments that the values for the balance, which comprises the measured activity of the carcass less the skeleton but including skin, blood, fat, and muscle, were higher than might be expected from the measured values of the samples of these tissues. This phenomenon has been encountered in other experiments in which the radioelements were poorly absorbed following intramuscular injection. It is very probable that this effect was due to the extravasation or movement by lymphatic drainage of a small fraction of the administered dose above the point where the injected leg was separated from the rest of the carcass.

The lung studies, as mentioned before, indicate that the retention of zirconium by the lungs following intrapulmonary administration is the highest for all of the fission products. Columbium has been shown to be the next most tenaciously retained fission product by the lungs. Very possibly the high degree of retention of zirconium at the site of administration in the intraperitoneal, intramuscular, and intrapulmonary studies is due to the formation of the very insoluble zirconium phosphate.

METABOLISM OF Y^{88} WITHOUT CARRIER FOLLOWING INTRAMUSCULAR AND INTRAPULMONARY ADMINISTRATION

In earlier reports, a series of detailed experiments describing the metabolism of Y^{88} following intraperitoneal administration have been presented (CH-379, CH-498). In addition, a few very preliminary experiments were included concerning the retention of Y^{88} by the lung following intrapulmonary administration. This report presents a series of intramuscular and intrapulmonary studies with Y^{88}.

Method

These studies were made because of the somewhat unsatisfactory results obtained with Y^{88} following intraperitoneal injection due to the apparent adsorption of a considerable proportion of the administered activity upon the surfaces of the intraperitoneal organs. Four groups of three animals each received, by intramuscular injection into the left thigh, 20μc of carrier-free Y^{88} as YCl_3 in a

solution of isotonic sodium chloride at pH 2.7. A second series of five groups received this material by intrapulmonary administration. The method employed for the preparation of Y^{88} has been described in report CH-379. The intramuscular groups were sacrificed at 1, 4, 16, and 64 days, and the lung series at 1, 4, 21, 32, and 64 days. The samples of tissue and excreta were collected and ashed and measured by the same procedures reported earlier, CH-379.

Results

The experimental data obtained for the intramuscular experiments are shown in Table 6. It will be seen that the skeleton was the principal organ of deposition for Y^{88}. From 50 to 60% of the absorbed dose was accumulated and retained by the skeleton.

It is of interest to note that the uptake by the liver of Y^{88} following intramuscular injection is much less than noted for the other rare earths, (La, Ce, Pr.), at the corresponding time intervals. The uptake by the other soft tissues of Y^{88} does not show a striking difference from the other rare earths. Moreover, the intraperitoneal studies with Y^{88} at the 4, 16, and 64-day intervals agree quite well with the corresponding values for the intramuscular experiments with Y^{88} except for, of course, the intraperitoneal organs. The excretion rate of Y^{88} following intramuscular injection is shown in Figures 2 and 3. These observed values for the intramuscular studies are comparable to those noted in the earlier intraperitoneal experiments. It might be noted, however, that the rate of elimination seemed to be greater following intraperitoneal injection. This observed difference between the two routes of administration is probably not of significant importance.

The results of the intrapulmonary experiments on Y^{88} are shown in Table 7. It may be noted that during the earlier phases of the experiments a considerable proportion of the administered material was retained by the lungs. However, at the end of 32 and 64 days, most of the retained activity in the lungs was apparently absorbed and deposited in the skeleton. The pulmonary retention of yttrium is significantly less than has been noted for cerium, and praseodymium. These in turn show lower values of pulmonary retention than have been noted for zirconium, columbium, and ruthenium.

DISTRIBUTION OF CARRIER-FREE $Ce^{>140}$ FOLLOWING INTRAMUSCULAR AND INTRAPULMONARY ADMINISTRATION

Earlier studies with $Ce^{>140}$, which were reported in CH-848, were not completely satisfactory due to the fact that most of the parenteral experiments were intraperitoneal in type and only a limited number of lung experiments were made at that time. In the following discussion a more complete series of lung experiments as well as extensive intramuscular studies are presented.

Method

A solution of $Ce^{>140}$ without carrier in the form of $CeCl_3$ in isotonic sodium chloride solution at pH 2.7 was administered by intramuscular injection to four groups of three animals each. A second series of four groups received this material by intrapulmonary administration. The $Ce^{>140}$ was prepared by the method described in report CH-848, and each animal received 5 cc of $Ce^{>140}$. The animals in both series were sacrificed at intervals of 1, 4, 16 and 64 days. The samples of tissues and excreta were collected, ashed, and measured as has been described in the earlier reports.

Results

Table 8 and Figures 4 and 5 present the results of the intramuscular studies with $Ce^{>140}$. With the exception of the intra-abdominal organs, the distribution of $Ce^{>140}$ in the tissues are very similar to those noted for the intraperitoneal studies. It is of interest to observe that in the earlier intervals a very large proportion of the absorbed activity is present in the liver. The kidney and spleen are found to be the next most active of the soft tissues. The fraction remaining unabsorbed at the site of injection

Table 6. Distribution of Y^{88} without carrier following intramuscular administration

	One day		Four days		Sixteen days		Sixty-four days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.007	.009	.042	.047	.036	.033	.013	.013
Liver	.70	.088	3.79	.30	1.22	.11	.36	.038
Kidney	.19	.10	1.61	.60	1.48	.54	.45	.19
Testes	.010	.003	.077	.020	.080	.027	.054	.027
Spleen	.017	.023	.23	.18	.24	.20	.11	.14
Muscle[1]	.18	.0018	1.45	.010	2.04	.015	.54	.004
Skin[2]	.19	.0045	3.80	.090	2.51	.060	2.02	.048
Stomach	.021	.006	.16	.044	.081	.013	.032	.016
Sm. intestine	.12	.011	.35	.027	.23	.023	.076	.009
Lg. intestine	.011	.013	.027	.062	.037	.035	.008	.015
Bone[3]	4.29	.24	42.77	1.98	55.06	2.93	59.83	1.77
Brain	.002	.001	.012	.008	.015	.009	.010	.006
Lungs	.018	.012	.12	.058	.13	.068	.092	.039
Fat	---	.004	--	.038	--	.05	---	---
Blood[4]	.097	.005	.16	.007	.13	.005	.017	.0007
Adrenals	.0006	.009	.004	.082	.006	.11	.002	.039
Lymph nodes	---	.003	---	.013	---	.068	---	.048
Feces[5]	---	.042	---	.047	---	.042	---	.012
Unab. in left leg	98.76	---	36.07		19.67		6.30	
Balance[6]	1.46		8.57		5.69		3.68	
Urine	.29		6.47		7.64		12.87	
Feces	.37		10.21		12.01		17.09	
Recovery	106.27%		110.51%		103.62		100.98%	

[1] Muscle estimated as 45% of total body weight.

[2] Skin estimated as 42 grams.

[3] Measured value for entire skeleton.

[4] Blood estimated as 8% of total body weight.

[5] Specimen of feces removed from large intestines at time of sacrifice.

[6] Balance is measured value for carcass less skeleton but includes skin, blood, and muscle.

Table 7. Distribution of retained activity following intrapulmonary administration of Y^{88} without inert carrier.

	1 day		4 days		21 days		32 days		64 days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.30	.29	.06	.07	.11	.07	.04	.03	.08	.08
Liver	.95	.074	3.21	.26	1.47	.13	.78	.051	.42	.029
Kidney	.56	.22	2.03	.73	.99	.37	1.20	.39	.50	.16
Spleen	.054	.050	.14	.13	.16	.16	.28	.19	.20	.18
Muscle[1]	---	.012	--	.09	--	.024	--	.006	--	.01
Skin[2]	omitted	---	omitted	--	1.13	.027	2.16	.051	1.50	.020
G-I tract	---	- --	--	--	.63	.04	.41	.03	.33	.009
Bone[3]	9.64	.48	38.99	2.12	72.44	3.33	85.20	3.89	83.4	3.30
Lungs	82.63	34.83	45.09	22.99	16.91	8.79	2.67	1.60	6.44	2.85
Balance[4]	5.74		13.69	--	5.93	--	6.89	--	7.31	--

[1] Muscle calculated on basis of 45% of total body weight.
[2] Animals skinned, measured value for entire skin.
[3] Measured value for entire skeleton.
[4] Measured value for remaining carcass less skin and skeleton but including blood and muscle.

was very similar to that noted at the corresponding time interval for Y^{88}. However, it is interesting to compare the uptake of the skeleton of these two rare earths, the value for yttrium being approximately twice as great. The uptake by the skeleton of cerium is quite similar to that observed for lanthanum and praseodymium.

The elimination of $Ce^{>140}$ following intramuscular administration was very similar to the observed results following intraperitoneal injection. It will be noted that for the first eight days following intramuscular administration the daily rate of excretion of $Ce^{>140}$ grew to a maximum and then decreased at a rate comparable to that noted in the intraperitoneal studies. This effect may have been due to the rather large fraction remaining unabsorbed for the first few days at the site of injection. Otherwise, no significantly important difference apparently exists in the elimination of carrier-free cerium by these two routes of administration. In view of the fact that one of the two long-lived radioactive cerium isotopes has half-life of 340 days, it is obvious that it will be necessary to initiate some more extended animal studies in order to determine whether the rate of elimination of carrier-free cerium becomes less after a period of several months.

The intrapulmonary experiments indicate that carrier-free cerium is retained by the lungs to a somewhat higher degree than was observed for carrier-free yttrium. The distribution of the absorbed fraction was comparable to the corresponding values observed in the intramuscular experiments.

Incomplete radioautographic experiments have been reported earlier and at present more extensive studies are in progress and will be presented later.

DECONTAMINATION STUDIES WITH THE PRODUCTS OF NUCLEAR FISSION

Those exposed to the products of nuclear fission are in constant danger of contamination with highly radioactive material. For the most part, the radioactive elements involved have such short half-lives that the natural radioactive decay is a far more important factor in reducing the radiation than any possible therapeutic measures.

Table 8. Distribution of $Ce^{>140}$ without carrier following intramuscular administration.

	One day		Four days		Sixteen days		Sixty-four days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.064	.075	.052	.070	.039	.050	.029	.045
Liver	14.78	2.05	22.03	3.77	8.09	.99	2.56	.47
Kidney	1.29	.66	1.47	.85	.76	.42	.26	.19
Testes	.079	.029	.042	.018	.035	.013	--	--
Spleen	.15	.18	.14	.22	.12	.16	.14	.31
Muscle[1]	1.04	.011	.62	.0075	.80	.0076	1.84	.023
Skin[2]	1.72	.041	2.45	.058	1.58	.038	.54	.013
Stomach	.17	.091	.14	.080	.12	.049	.084	.036
Sm. intestine	.37	.051	1.40	.18	.27	.023	.095	.016
Lg. intestine	.046	.051	.018	.075	.012	.035	.011	.027
Bone[3]	12.47	.65	19.26	.82	20.24	1.05	25.13	1.69
Brain	.005	.004	.005	.004	.003	.002	.007	.005
Lungs	.13	.077	.10	.085	.12	.070	.086	.058
Fat	--	.060	--	.018	--	---	---	.013
Blood[4]	.34	.020	.073	.005	.02	.001	.030	.002
Feces[5]	--	---	---	.53	--	---	---	---
Adrenals	.007	.15	.007	.13	.004	.088	.013	.12
Lymph nodes	--	.11	---	.072	---	.035	---	.050
Unab. in left leg	59.09	--	35.64	---	22.94		10.67	---
Balance[6]	4.62	.031	4.66	.035	3.49	.023	2.52	.021
Urine	.86		1.18		1.58		1.65	
Feces	1.09		2.32		26.55		58.49	
Recovery	95.22%		88.56%		84.37%		101.74%	

[1] Muscle estimated as 45% of total body weight.

[2] Skin estimated as 42 grams.

[3] Measured value for entire skeleton.

[4] Blood estimated as 8% of total body weight.

[5] Specimen of feces removed from large intestines at time of sacrifice.

[6] Balance is measured value for carcass less skeleton but includes skin, blood, and muscle.

Table 9. Distribution of retained activity following intrapulmonary administration of $Ce^{>140}$ without inert carrier.

	One day		Four days		Sixteen days		Sixty-four days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart			.10	.14	.056	.092	.10	.15
Liver	14.6	1.73	16.3	1.66	18.2	2.53	7.04	1.43
Kidney	.58	.35	1.70	.92	.77	.47	.66	.53
Spleen	.048	.071	.080	.12	.17	.27	.20	.50
Muscle	.75	.010	2.80	.036	1.36	.017	3.38	.059
Skin[1]	omitted	omitted	2.17	.082	1.11	.045	2.42	.12
G-I. tract[2]	omitted	omitted	4.00	.20	2.81	.11	.93	.089
Bone[3]	14.0	.55	21.2	1.53	37.6	2.40	74.6	4.49
Lungs	66.5	52.7	49.5	29.3	35.3	21.6	9.43	8.76
Balance[4]	4.01	.046	4.25	.046	4.42	.045	4.24	.055

[1] Animals skinned, measured value for entire skin.

[2] G-I tract removed and assayed as a unit.

[3] Measured value for entire skeleton.

[4] Measured value for remaining carcass less skin and skeleton but including blood and muscle.

However, certain radioactive isotopes of strontium, yttrium, and cerium (and to a much smaller degree barium), have such long half-lives that they present a grave problem of chronic radiation poisoning in contaminated individuals. Further, these elements tend to localize in the mineral fraction of bone, from which they are dislodged only with the greatest difficulty. The gravity of the problem is increased by the biologically active character of the radiations involved, and the localization in close proximity to the radiosensitive bone marrow. In many respects the problem resembles that of radium poisoning, both in its preventive aspects and in the difficulty of obtaining effective therapy.

Although all four elements become distributed throughout the tissues of the body following intrapulmonary or intramuscular injection, only the strontium and barium are absorbed from the intestinal tract. Thus radiostrontium presents the chief hazard when active material is inadvertently swallowed, or when food and water is contaminated. Much of the initial work was done with radiostrontium for this reason, and because it was felt that due to the close parallel with calcium, such experiments might yield valuable information on the metabolism of bone.

The problem of decontamination was approached from three angles:

1) Factors affecting the absorption of orally administered radiostrontium.

2) Factors affecting the excretion of radiostrontium, radioyttrium, and radiocerium immediately after they have been introduced into the body.

3) Long term excretion studies with radiostrontium, radioyttrium, and radiocerium, carried out over a period of several months, to determine the rate of elimination of these radioactive isotopes, and the influence upon it of various experimental regimens.

The experiments were carried out on rats, usually in groups of five to reduce the effect of individual variations. The results are given as a per cent of the administered dose, corrected to one hundred, and expressed as the mean value plus or minus the mean deviation.

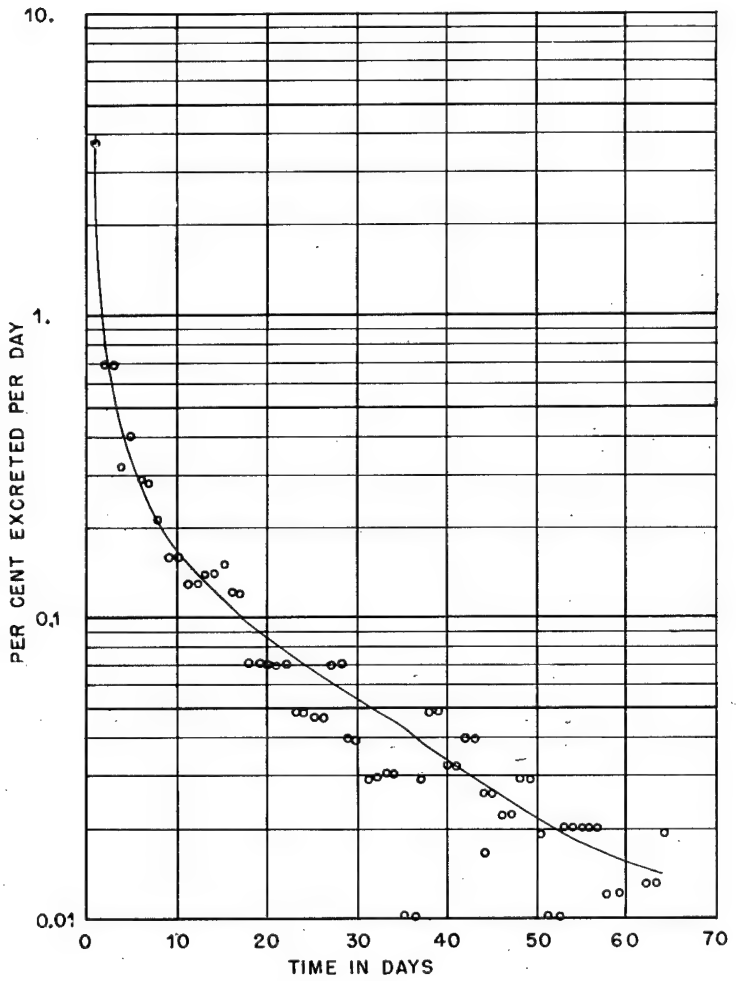

Figure 2. Urinary excretion of Y^{88} without carrier following intramuscular administration.

Factors Affecting the Absorption of Orally Administered Radiostrontium

It was soon discovered that once the radiostrontium had been absorbed, removal was very difficult. Accordingly, various procedures were investigated to determine whether they might effectively reduce the absorption of radiostrontium from the intestinal tract. The effect of certain absorbing agents was investigated, first in vitro, and later in the intact animal. The values of cathartics and other agents were studied. Next, experiments were carried out to determine the influence of the calcium content of the diet. These experiments were particularly interesting because of the low level of calcium common in the average human diet.

Adsorption of Radiostrontium in vitro

Various adsorbing agents were added to solutions containing trace amounts of radiostrontium. The solutions were shaken, made to volume, and filtered. The amount of unadsorbed radiostrontium in the filtrate was determined. The effect of adding acid and alkali was also investigated. The results are shown in Table 10.

Table 10. Adsorption of radiostrontium in vitro.

Adsorbing agent		% Sr* unadsorbed (in filtrate) (1)	(2)
0.2% tricalcium phosphate	neutral	106	93
	0.5% disodium phosphate	0.1	0.1
	0.2% sodium bicarbonate	2.1	0.1
	N/100 hydrochloric acid	106	108
0.1% columbic acid (freshly pptd.)	neutral	20.1	18.8
	0.2% sodium bicarbonate	1.5	2.3
	N/100 hydrochloric acid	75	68
0.1% bentonite	neutral	76	70
	0.2% sodium bicarbonate	77	68
	N/100 hydrochloric acid	87	84

Observations — From these results, it appears that the only effective adsorption of trace amounts of radiostrontium occurred with tricalcium phosphate or columbic acid in alkaline solution.

Effect of Adsorbing Agents on the Adsorption of Sr*

The difficulty in removing radiostrontium from the body once it has been adsorbed has already been mentioned. The following experiments were undertaken to determine how effective adsorbing agents might be in reducing the intestinal adsorption if they were administered soon after the dose of radiostrontium.

Rats, in groups of five were each given a dose of 0.2 mg Sr* by stomach tube. After the desired time interval, the adsorbing agent was given, also by stomach tube. The animals were sacrificed after 4 days, and the intestinal tract with its contents was removed and added to the excreta.

Table 11. Effect of adsorbing agents on the intestinal absorption of radiostrontium.

Agent	No. of rats	Treatment	Time lapse	% dose of Sr* absorbed and retained
(1) Control	5	None		12.7 ±2.9
	5			9.2 ±1.8
	5			11.8 ±3.0
(2) Tricalcium phosphate	5	2 cc 10% tricalc. phosphate	10 min	9.8 ±1.9
	5	5 cc 5% tricalc. phosphate in 10% sodium bicarbonate	10 min	9.8 ±3.5
	5	2 cc 5% tricalc. phosphate in 12 1/2 disodium phosphate	0 min	3.2 ±1.0
	5	" "	15 min	4.0 ±0.9
	5	" "	2 hr	10.0 ±3.1
	5	" "	4 hr	7.8 ±2.2
	5	" "	8 hr	8.0 ±2.2
	5	" "	24 hr	7.3 ±0.7
(3) Columbic acid	5	1 cc freshly pptd. columbic acid in 10% sodium bicarb.	10 min	8.6 ±2.5

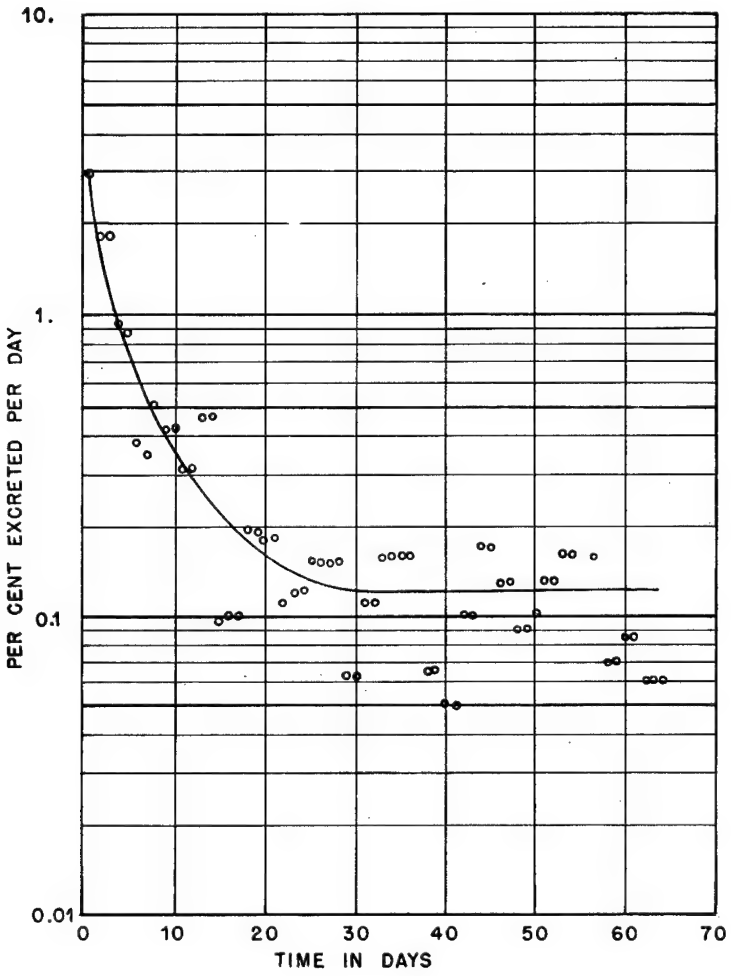

Figure 3. Fecal elimination of Y^{88} without carrier following intramuscular administration.

The per cent of the administered dose of Sr* absorbed and retained by the animals is shown in Table 11. The values given are the averages for the group, plus or minus the mean deviation.

Observations—The only significant reduction in the absorption of Sr* occurred when a suspension of tricalcium phosphate in a solution of disodium phosphate was administered almost immediately after the dose of Sr*.

Effect of Other Procedures on the Intestinal Absorption of Radiostrontium

Experiments similar to the preceding were performed using cathartics, alkaline solutions, and other agents in an attempt to reduce the absorption of orally administered Sr*. The results are given in Table 12.

Observations—From these results it is evident that neither cathartics, alkaline solutions nor carrier strontium causes any significant reduction in the absorption of radiostrontium.

Effect of Fasting on the Absorption of Sr* from the Intestinal Tract

The effects of the food intake and fasting were investigated in the following experiment on three

Table 12. Effect of treatment on the absorption of orally administered radiostrontium.

Group	Treatment	Time lapse	No. of rats	% dose of Sr* absorbed and retained
(1) Control	None		5	12.7 ± 2.9
	None		5	9.2 ± 1.8
	None		5	11.8 ± 3.0
(2) Cathartics	a) 2 cc 10% disodium phosphate	10 min	5	11.0 ± 2.5
	2 cc 10% disodium phosphate	8 hr	5	12.6 ± 2.3
	b) 2 cc 25% magnesium sulfate	15 min	5	10.3 ± 1.7
	2 cc 25% magnesium sulfate	8 hr	5	9.2 ± 2.5
(3) Silicate	2 cc 25% sodium silicate	15 min	5	15.6 ± 4.6
	2 cc 25% sodium silicate	8 hr	5	12.7 ± 3.2
(4) Bicarbonate	5 cc 10% sodium bicarbonate	10 min	5	10.3 ± 1.4
(5) Carrier Sr	1 cc 10% strontium lactate	10 min	10	9.7 ± 2.5
	1 cc 10% strontium lactate at 1 cc 25% disod. phosphate at	15 min 30 min	5	6.9 ± 1.4
	1 cc 10% strontium lactate and 2 cc 10% tricalc. phosphate in 12 1/2% disodium phosphate	10 min	5	8.2 ± 2.0

Table 13. Effect of fasting on the absorption of Sr*.

No. of rats	2 days prior to administration of Sr*	2 days following administration of Sr*	% dose of Sr* absorbed
5	Fed stock diet	Fed stock diet	14.0 ± 0.8
5	Fed stock diet	Fasted	21.2 ± 1.5
5	Fasted	Fed stock diet	16.5 ± 2.5
4	Fasted	Fasted	18.0 ± 4.2

month old female rats reared on stock diet. The animals were fasted for a period of two days prior to or following the oral administration of 0.2 mg Sr*. They were sacrificed after four days. The results obtained are shown in Table 13.

Observations—The animals which had been fasted showed an increase in the absorption of Sr*, whether they were fasted before or following the administration of the radioactive dose.

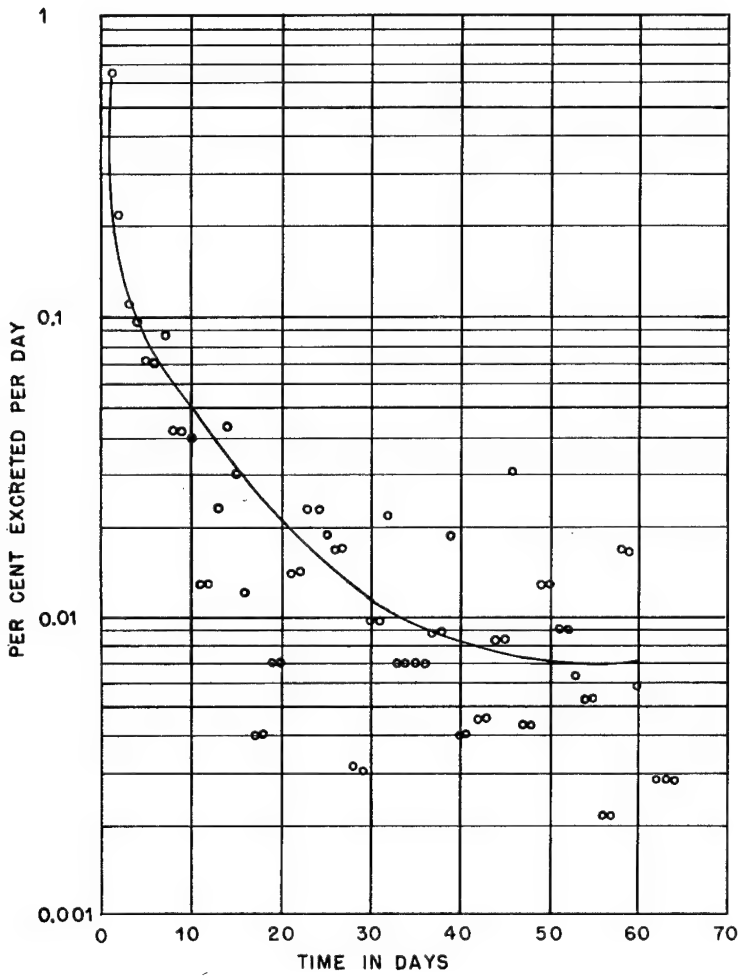

Figure 4. Urinary excretion of $Ce^{>140}$ without carrier following intramuscular administration.

Effect of Age on the Absorption of Sr*

Since the age of the animal is an important factor in determining the activity of calcium metabolism, it was decided to investigate the effect of this on absorption, using the methods described. The following results were obtained:

a) Young rats, two months old, weighing 100 to 150 grams, absorbed and retained 16.4 $\pm$ 5.0% of the dose of Sr*.

b) Old rats, eight to twelve months old, weighing 300 to 400 grams, absorbed 7.6 $\pm$ 5.0% of the dose of Sr*.

Observations — As might be expected, young growing rats absorb and retain almost twice as much radiostrontium as do old rats.

Effect of the Calcium Content of the Diet on the Absorption of Sr*

The failure of the obvious oral agents listed to produce any effective reduction in the absorption of radiostrontium from the intestinal tract necessitated a new approach to the problem. It appeared

probable that the calcium content of the diet would be an important factor in determining absorption. This was confirmed when early experiments indicated a tremendous increase in the absorption of radiostrontium by animals on a low calcium diet. The experiments were then repeated on groups of animals which were maintained for several weeks on synthetic diets which varied in their calcium content. These diets had the following composition:

commercial casein	25.0%	sodium chloride	0.91%
fat (primex)	15.0%	disodium phosphate	0.91%
yeast (dry power)	10.0%	potassium chloride	1.15%
cod liver oil	2.0%	magnesium sulfate	0.12%
sucrose	40.0 – 45.0%	ferric citrate	0.12%

and calcium carbonate sufficient to produce the desired calcium content

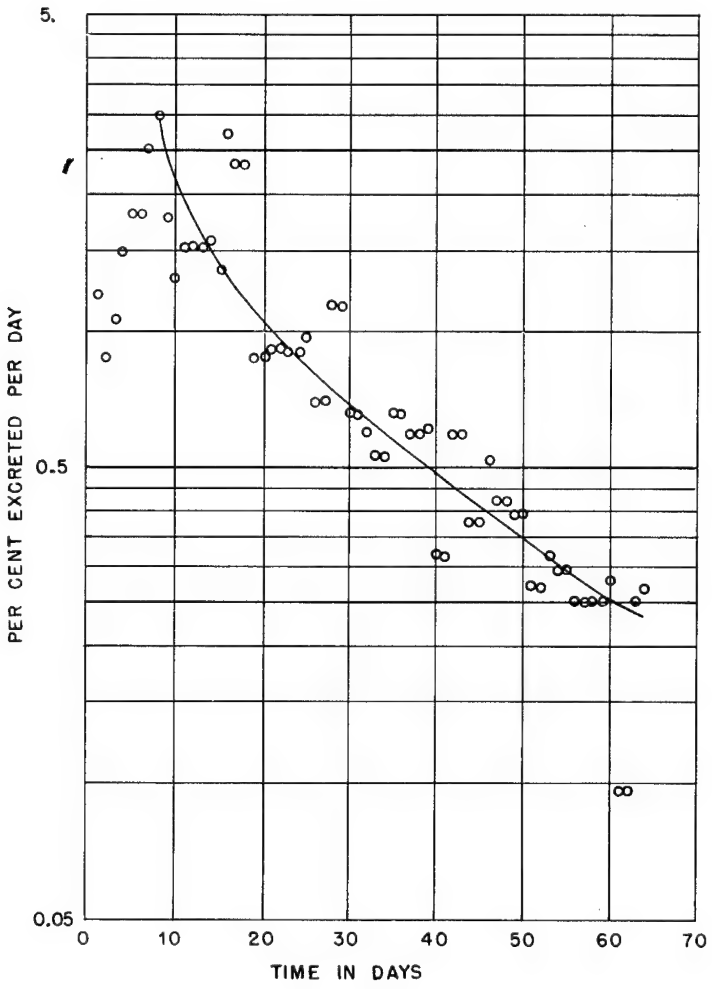

Figure 5. Fecal excretion of $Ce^{>140}$ without carrier following intramuscular administration.

The animals, in groups of five, were maintained on these diets for three weeks. They were then given 0.2 mg Sr* by stomach tube, and the excreta were collected for four days, at which time the animals were sacrificed. The per cent of the dose of Sr* absorbed and retained by the animals was corrected to one hundred and averaged for each group. These values are presented in Table 14, and are plotted against the calcium content of the diet in Figure 6.

Table 14. Effect of the calcium content of the diet on the absorption of radiostrontium.†

% calcium in diet	% $CaCO_3$ in diet	No. of rats	% dose of Sr* absorbed and retained
0	0	10	59.2 ± 8.0
0.02	0.05	4	59.9 ± 3.9
0.04	0.10	9	49.2 ± 8.9
0.08	0.20	5	42.9 ± 6.8
0.12	0.30	5	34.1 ± 7.8
0.16	0.40	5	40.9 ± 7.0
0.20	0.50	10	12.7 ± 5.6
0.40	1.00	5	8.1 ± 0.8
2.00	5.00	10	8.9 ± 4.3

† The per cent of the dose of radiostrontium absorbed and retained is shown plotted against the calcium content of the diet in Figure 6.

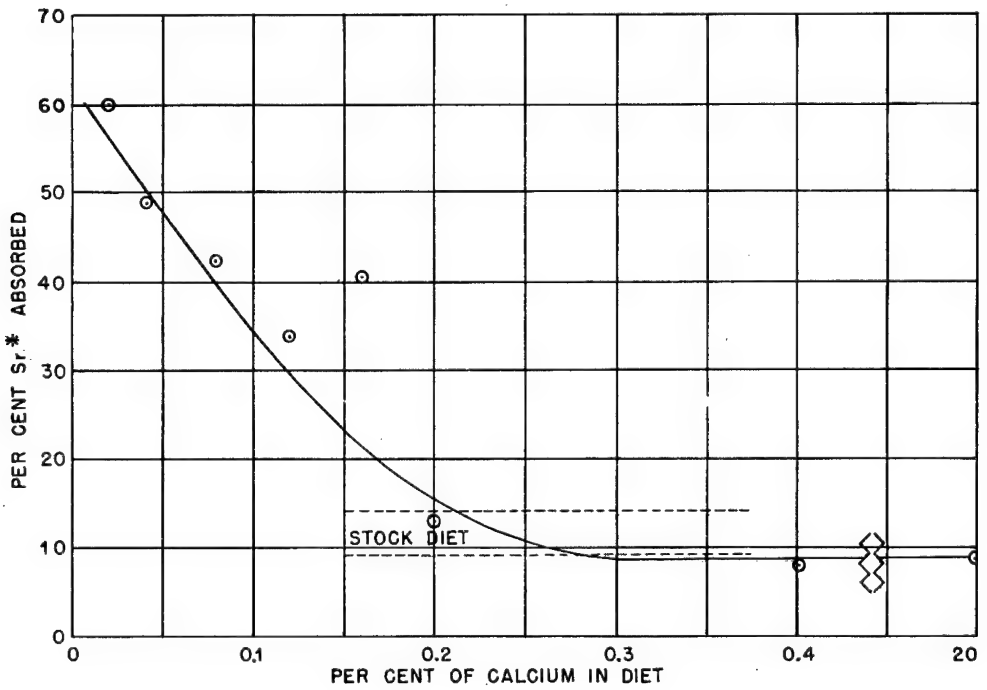

Figure 6. Effect of calcium content of diet on the absorption of Sr*.

Observations—The calcium content of the diet on which the animal has been maintained profoundly affects the absorption of Sr* from the intestinal tract. Rats maintained on a low calcium diet absorbed five to seven times as much Sr* as did those on adequate or high calcium diets. The critical level for the rat appears to be in the neighborhood of 0.2 per cent calcium. These findings are particularly interesting because many human diets are very low in calcium. The preventive value of supplementing the diet with calcium is evident. This might be accomplished by increased consumption of milk and dairy products, by regular administration of calcium in capsules or tablets, or by use of calcium-fortified bread.

Effect of Carrier Strontium on the Intestinal Absorption of Sr* by Rats Maintained on a Diet Low in Calcium

Since it was felt that the great increase in Sr* absorption by the rats on a low calcium diet might be due solely to the low calcium concentration locally in the intestinal trace, experiments were carried out in which large amounts of nonradioactive strontium were administered to the animals with the dose of Sr* or shortly after it.

Three month old rats were maintained for three weeks on the synthetic diet described previously supplemented by 0.1% calcium carbonate (0.04% calcium). They were then given 0.2 mg radiostrontium by stomach tube, followed by 50 mg "carrier" strontium as the lactate. The animals were sacrificed at four days. The results obtained are given in Table 15.

Observations—These results, in agreement with earlier experiments on rats on stock diet, indicate that "carrier" strontium has only a small effect on the absorption of radiostrontium, and then only when mixed with the dose. It would appear that the low calcium concentration in the intestinal tract of animals on a low calcium diet is not the main factor responsible for the increased absorption. This would indicate that the calcium supplement to the diet need not be continuous, but could be given once a day.

Summary

The following conclusions are drawn from experiments on over 250 rats on the effects of various factors on the absorption of Sr*.

1. Adsorbing Agents. Tricalcium phosphate, columbic acid, and bentonite were investigated and found to have little effect. An exception was the 5% suspension of tricalcium phosphate in 12 1/2% disodium phosphate solution, which did reduce absorption, but only when given immediately after the Sr*.

2. Cathartics and Other Agents. Cathartic doses of magnesium sulfate and disodium phosphate, alkaline solutions of sodium silicate and sodium bicarbonate, and "carrier" solutions of nonradioactive

Table 15. Effect of "carrier" strontium on the absorption of Sr* by rats on low calcium diet.

	Treatment	Time Lapse	No. of rats	% dose of Sr* absorbed
(1)	Control, no treatment		12	35.0 ± 9.6
(2)	50 mg Sr mixed with Sr* before administration	0	6	23.6 ± 3.1
(3)	50 mg Sr as lactate	15 min	9	30.9 ± 6.0
		1 hour	5	32.8 ± 3.2
		4 hours	5	34.6 ± 2.4

strontium all had no significant effect on the absorption of Sr*.

3. Fasting. Rats fasted for two days prior to or following the administration of Sr* showed an increase in absorption.

4. Age. Young growing animals absorbed and retained almost twice as much Sr* as did the adult animals.

5. Calcium Content of the Diet. The calcium content of the diet had a profound effect on the absorption of Sr*. Rats on a low calcium diet absorbed 5 to 7 times as much Sr* as did those on an adequate or high calcium diet. In the rat, the critical level appears to be in the neighborhood of 0.2% calcium.

6. "Carrier" Strontium. Large doses of carrier strontium (50 mg) had little effect on the absorption of Sr* by animals on stock diet, or on a diet low in calcium.

The relative ineffectiveness of the measures investigated emphasizes the importance of prevention. The best supplementary measure to reduce the hazard of Sr* absorption is the maintenance of an adequate or high level of calcium in the diet.

EXCRETION OF INJECTED RADIOSTRONTIUM, RADIOYTTRIUM, AND RADIOCERIUM

In most cases, the problem of decontamination centers around methods for increasing the elimination of the radioactive materials after they have been introduced into the body. In the following experiments, the influence of various factors on the initial excretion of injected Sr* (and later Y* and Ce*) was investigated. The experimental treatment was commenced immediately after injecting the radioactive dose. Urine and feces were collected and analyzed separately, and the animals were sacrificed at the end of four days.

Effect of Age

Since the activity of calcium metabolism declines with age, it was felt that this might have an important effect on the behavior of injected Sr*. A dose of 0.2 mg Sr* was injected intraperitoneally into young and old rats. The results are summarized in the following tabulation.

A. Young female rats, two months old, weighing 100 to 150 grams. (4)

% dose of Sr* in:	Urine	14.4 ± 2.1
	Feces	12.0 ± 1.9
	Carcass	73.7 ± 3.3

B. Old male rats, eight to twelve months old, weighing 300 to 400 grams. (5)

% dose of Sr in:	Urine	26.5 ± 5.5
	Feces	38.7 ± 7.8
	Carcass	34.8 ± 6.3

Observations—The growing rats retained twice as much Sr* as did the adult rats, reflecting the more active calcium metabolism in the former.

Effect of the Injection of Nonradioactive "Carrier" Strontium

The value of nonradioactive "carrier" strontium as an agent to dilute and wash out the radioactive strontium was investigated in the following experiments. Young adult male rats on the regular stock diet were used. A dose of 0.2 mg of radiostrontium was injected intraperitoneally, followed by injections of a 6.8% solution of strontium lactate (2.5% Sr). A summary of the results is given in Table 16.

Table 16. Effect of carrier strontium on the excretion of Sr*.

Treatment	Time lapse	No. of rats	% dose of Sr*	
			Excreta	Carcass
Control, no treatment		9	28.2 ± 4.0	71.8 ± 4.6
60 mg Sr in a single dose (toxic — 2 died)	15 min	5	40.1 ± 10.0	60.0 ± 9.3
20 mg Sr every 4 hours for 6 doses (toxic — 3 died)	15 min	5	39.1	60.9
10 mg Sr every 4 hours for 6 doses (not toxic — all thrived and gained weight)	15 min	5	42.5 ± 7.8	57.4 ± 9.5
	8 hours	5	28.9 ± 1.7	71.3 ± 1.7
	24 hours	5	32.2 ± 9.4	68.1 ± 9.4
	48 hours	5	23.4 ± 2.2	76.4 ± 4.2

Observations — The single dose of 60 mg Sr, or the repeated dose of 20 mg every four hours appeared to be toxic for the animals, causing loss of weight, hyperirritability, and a number of fatalities. The animals which received 10 mg Sr every four hours showed no ill effects. This appears to be the maximum safe therapeutic dose for the rat. This treatment increased the excretion of Sr* almost 50 per cent when given immediately after the radioactive dose, but was ineffective after a lapse of only eight hours. This suggests a very rapid stabilization of the Sr* in bone, from which it may no longer be easily washed out with "carrier" strontium.

Effect of Parathormone on the Excretion of Sr*

Parathormone is a well-established therapeutic agent in lead and radium poisoning because of its action in promoting bone resorption and in increasing urinary excretion of calcium. These experiments were undertaken to determine how effective parathormone might be when given in large doses immediately after the Sr* was injected. The animals were sacrificed after four days. The results are summarized in Table 17.

Table 17. Effect of parathormone and strontium on the excretion of Sr*.

Treatment	No. of rats	% dose of Sr*		
		Urine	Feces	Carcass
Control	5	27.5 ± 1.3	36.0 ± 2.8	36.4 ± 1.3
Parathormone, 100 units subcutan., daily	5	32.4 ± 3.5	35.8 ± 1.8	31.9 ± 1.6
Strontium, 10 mg injected I.P. daily	5	33.8 ± 4.1	38.8 ± 4.0	27.2 ± 3.0
Strontium, 10 mg I.P., daily Parathormone, 100 units subcutan., daily	5	32.7 ± 3.7	36.4 ± 4.3	30.9 ± 2.0

Observations — Parathormone and "carrier" strontium, in the doses used, caused an increase in the urinary excretion of Sr*, and a small decrease in its retention. The dose of parathormone used was toxic, and caused loss of weight. Its value as an acute method of therapy is questionable. This does not, however, rule out the possibility that it may have a beneficial effect when given in small doses over long periods as a chronic treatment.

Effect of Irradiated Ergosterol and A.T. 10

Massive doses of certain irradiated sterols are known to cause decalcification of bone and an increased urinary excretion of calcium. The effect of such therapy on the excretion of Sr* was studied in the following experiments. Adult female rats injected intraperitoneally with Sr* were given massive doses of irradiated ergosterol or A.T. 10 by mouth at 0, 1, 2, and 4 days. They were sacrificed at eight days. The results are given in Table 18.

Table 18. Effect of irradiated sterols on the excretion of radiostrontium.

Treatment	No. of rats	% dose of Sr*		
		Urine	Feces	Carcass
Control, no treatment	5	27.0 ± 2.3	33.9 ± 0.6	39.1 ± 2.0
Irradiated ergosterol, 100,000 units; at 0, 1, 2, and 4 days	5	30.0 ± 3.7	29.2 ± 3.3	40.7 ± 4.6
Hytakerol (A.T. 10), 0.5 cc at 0, 1, 2, and 4 days	5	33.6 ± 2.4	24.7 ± 3.1	41.9 ± 1.5

Observations — Massive toxic doses of irradiated ergosterol or of Hytakerol caused no significant change in the retention of injected Sr*, the small increase in urinary excretion being more than compensated for by the decrease in the feces.

Effect of the Calcium Content of the Diet on the Excretion of Sr*, Y*, and Ce*

The calcium balance in the animal is closely related to the calcium content of the diet. The effect of this on the excretion of Sr*, Y*, and Ce* was studied in young male rats. For the two week period prior to administration of the radioactive dose, they were maintained on a synthetic diet high or low in calcium as described in the subsection beginning on the bottom of page 18 entitled "Effect of the Calcium Content of the Diet on the Absorption of Sr." They were continued on this diet for four days, and were then sacrificed.

The dose of 0.2 mg Sr* was given by intraperitoneal injection. The trace doses of Y* and Ce* were administered in isotonic saline at pH 2.3 by intramuscular injection into the right calf. The amount of Y* or Ce* in this leg was compared to that of the opposite side to determine the amount which had been absorbed from the site of injection. The results obtained are shown in Table 19.

Observations — The rats on the low calcium diet showed an increase in the retention of Sr* due largely to a decrease (three fold) in the urinary excretion. There is a suggestion of a similar effect in the case of Ce*. This is in harmony with the known retention of calcium by deficient animals.

No significant difference was observed in the retention of Y* or Ce*. It is interesting to observe that Ce*, in contrast to Y*, appears to localize to a considerable extent in the liver. On the other hand, the urinary excretion of Y* is much greater than that of Ce*.

Table 19. Effect of the calcium content of the diet on the excretion of Sr*, Y*, and Ce*.

Dose	Calcium diet	% dose absorbed	% of Absorbed Dose			
			Liver	Urine	Feces	Carcass
Sr*, I.P.	Low Ca (0%)	100%		5.5 ± 0.6	8.8 ± 1.4	85.7 ± 1.6
	High Ca (2.0%)	100%		16.3 ± 5.4	8.9 ± 4.3	74.8 ± 5.8
Y*, I.M.	Low Ca (0%)	77.6 ± 4.3	1.7 ± 0.4	18.8 ± 3.7	2.3 ± 1.3	75.3 ± 3.3
	High Ca (2.0%)	83.3 ± 2.0	2.4 ± 0.3	14.1 ± 1.8	5.5 ± 1.0	77.6 ± 1.2
Ce*, I.M.	Low Ca (0%)	57.3 ± 1.1	27.4 ± 6.0	2.9 ± 1.2	8.3 ± 1.6	61.4 ± 1.6
	High Ca(2.0%	59.4 ± 5.3	23.0 ± 2.8	6.8 ± 1.8	7.9 ± 1.7	62.5 ± 3.0

Summary

1. Age Effect. Young growing rats, in which calcification is active, retained over twice as much Sr* as did the old adult animals.

2. "Carrier" Strontium. Repeated doses of nonradioactive strontium increased the excretion of Sr* almost 50%, but only when the therapy was commenced immediately after the injection of Sr*.

3. Parathormone. Large doses of parathormone (at toxic levels) caused a small increase in the excretion of Sr*, but the value of this hormone in acute therapy is questionable.

4. Irradiated Sterols. Massive toxic doses of irradiated ergosterol or of Hytakerol had no effect on the retention of Sr*. The small increase in urinary excretion was more than balanced by a decrease in fecal elimination.

5. Calcium Content of the Diet. Rats on a low calcium diet showed a decrease in the urinary excretion of Sr* and Ce*, but the increased retention by these animals was small. No effect was observed with Y*.

LONG TERM STUDIES OF THE EXCRETION OF Sr*, Y*, AND Ce*

The preceding experiments indicate the difficulty in reducing the absorption of Sr*, or of increasing its elimination by short courses of treatment immediately after contamination. This reduces the problem once again to that presented by chronic radium poisoning. While continuing the investigations along the lines of the preceding experiments, attention has now been focussed on the aspect of chronic elimination of these radioactive isotopes.

Adult rats have been injected with large trace doses of Sr*, Y*, and Ce*, placed in individual metabolism cages, and the urine and feces have been collected for analysis every week. In this way, the rate of elimination of the radioactive material is being determined over a period of many months, and the effect of various chronic methods of treatment on this rate is being investigated. Five rats are used in each group. They are placed on the experimental regimen for four weeks and then are given four weeks on the control diet.

The following groups of rats are being studied:

a) Sr*. 20 rats. Each received 4 microcuries of Sr* by intraperitoneal injection.

b) Y*. 15 rats. Each received 2 microcuries of Sr* by intramuscular injection into the right calf. After three weeks, the right leg was amputated, to remove any unabsorbed Y* from the site of injection.

c) Ce*. 14 rats. Each received 2 microcuries of Ce* by intramuscular injection into the right leg. This leg was amputated after three weeks as in the case of the Y*.

These experiments have been under way for several months. The results will be presented in a later report.

CONCLUSIONS

The most effective means of reducing the absorption of Sr* from the intestinal tract is the maintenance of an adequate or high calcium intake. This may be accomplished by increased use of milk and dairy products, by taking medicinal calcium regularly, or by use of bread fortified with calcium. The important factor is apparently the general level of calcium intake rather than the amount present in the intestinal tract at the moment.

While most adsorbents, cathartics, and other agents tried proved ineffective in reducing the absorption of Sr*, a suspension of 5% tricalcium phosphate in 12 1/2% disodium phosphate solution appeared to be of value when given immediately after the Sr* was swallowed.

Fasting caused some increase in the absorption of Sr*.

None of the acute methods of therapy which were tried appeared to be very effective in increasing the elimination of Sr*. Large doses of nonradioactive strontium injected immediately after the dose of Sr* did increase the excretion, but it is unlikely that this treatment could be instituted soon enough to be effective.

The rate of elimination of Sr*, Y*, and Ce* is now being determined over long periods. The effect of various chronic methods of treatment on this rate is being investigated. It is hoped that these experiments may produce more effective methods of decontamination.

The importance of the preventive aspects of the problem is emphasized by the absence to date of any dramatic decontamination procedure.

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